Design and synthesis of potential inhibitors of LpxC

Rebeca J. Roldan, Kayla A. Wilson, Gene G. Lamanilao, Larryn W. Peterson, Mauricio Cafiero
Dept. of Chemistry, Rhodes College, Memphis TN, 38112

Potential inhibitors that mimic the natural substrate of UDP-(3-O-((R)-3-hydroxymyristoyl))-N-acetylglucosamine deacetylase, or LpxC, have been designed and synthesized. The enzyme is involved in the first committed step of the biosynthesis of Lipid A, an important part of lipopolysaccharide, which makes up the outer cell membrane of Gram-negative bacteria. When LpxC is inhibited, the production of Lipid A is halted and the virulence of the bacteria is reduced significantly. Using information found through computational study and analysis of its crystal structure, it was determined that the active site of LpxC contains three key regions: a zinc ion, a polar region, and a hydrophobic passage. This study focuses on the design and synthesis of analogs that include moieties that bind to the zinc and the hydrophobic region.